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Original Article

Evaluation of etiology, clinical and laboratory data of childhood arthritis

Çocukluk çağı artritlerinin etyolojik, klinik ve laboratuar verilerinin değerlendirilmesi

Ozge DEDEOGLU*, Eyup SARI, Saliha SENEL, Can Demir KARACAN

Sami Ulus Maternity and Child Health and Diseases Education and Research Hospital Ankara/TURKEY
Pamukkale University School of Medicine, Department of Biochemistry, Denizli/TURKEY

Abstract

Aim: The aim of the present study was to evaluate the etiologies, diagnostic approach, clinical and laboratory data of patients with arthritis in a Turkish tertiary care hospital in children.

Material and Methods: 306 hospitalized children aged between 7 months-18 years, diagnosed with arthritis were included in the study between 2008 – 2013. The medical records of patients were reviewed retrospectively.

Results: Of the patients, 51.6% were female, 48.4% were male. The average age was 118 months. Arthritis was symmetrical type in 29.4% of patients and asymmetrical type in 70.6%. The diagnoses of patients were Acute Rheumatic Fever/ Poststreptococcal reactive arthritis (ARF/PSRA) (39.2%), Collagen Tissue Disorders (CTD) (29%), Brucellar arthritis (13.4%), reactive arthritis (12.5%), septic arthritis (5.2%) and arthritis secondary to malignancy (0.7%), respectively. Of the patients with CTD; Juvenil idiopathic arthritis (JIA) was the most common in frequency (66.3%). Patellar joint involvement was the most common in frequency (62.4%). The mean ASO levels was significantly higher in patients with ARF/PSRA group [p=0.000]. Average leucocyte count of ARF/PSRA group was significantly higher than CTD group [p=0.000]. Average neutrophil percentage was significantly higher in ARF/PSRA group than brucellar arthritis group [p=0.000]. The mean duration of diagnosis and therapy was found to be significantly longer in patients with CTD [p=0.000]. All patients were cured except one patient with brucellar arthritis.

Conclusion: Arthritis can be a manifestation of multiple disease processes in children. Therefore, the clinician must consider a broad differential diagnosis. Detail history and physical examination with a clinical follow-up in addition to useful laboratory testing may help to establish the cause of arthritis in children.

Keywords: arthritis; children; etiology

Corresponding author*: Ozge Dedeoglu, Sami Ulus Maternity and Child Health and Diseases Education and Research Hospital Ankara/TURKEY
E-posta: ozgem.dr@gmail.com
ORCID: 0000-0002-7492-5255
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Öz

Amaç: Bu çalışmanın amacı üçüncü basamak olan bir sağlık kuruluşunda artrit tanısıyla takip edilen çocuk hastaların etyolojisi, tanısal yaklaşımı, klinik ve laboratuvar verilerinin değerlendirilmesidir.

Gereç ve Yöntemler: 2008 - 2013 yılları arasında, 7 ay-18 yaş arasında, hastanede yatarak tedavi gören 306 artrit tanılı çocuk çalışmaya dahil edildi. Hastaların tıbbi kayıtları retrospektif olarak incelendi.

Bulgular: Hastaların % 51,6'sı kız, % 48.4'ü erkekti. Yaş ortalaması 118 ay idi. Hastaların % 29.4'ünde simetrik, % 70.6'sında asimetrik tip artrit tespit edildi. Hastaların tanıları sırasıyla Akut Romatizmal Ateş/Poststreptokoksik reaktif artrit (ARA/PSRA) (% 39.2), Kollajen doku hastalığı (KDH) (% 29), brusella artriti (% 13.4), reaktif artrit (% 12.5), septik artrit (% 5.2) ve maligniteye bağlı artrit (% 0.7) idi. Kollajen doku hastalığı grubunda jüvenil idyopatik artrit (JİA) en sık görülen hastalık idi (% 66.3). Patellar eklem tutulumu en sık tutulan eklemdi (% 62.4). ARA / PSRA grubu olan hastalarda ortalama ASO düzeyleri yüksek bulundu [p = 0.000]. ARA / PSRA grubunun ortalama lökosit sayısı, KDH grubundan yüksekti [p = 0.000]. ARA / PSRA grubunda ortalama nötrofil yüzdesi brusella artriti grubundan daha yüksekti [p = 0.000]. KDH hastalarında ortalama tanı ve tedavi süresi daha uzun bulundu [p = 0.000]. Brusella artriti tanılı bir hasta hariç tüm hastalar sekelsiz iyileşti.

Sonuç: Artrit çocukluk çağında sistemik hastalık sürecinin bir bulgusu olabilir. Bu nedenle klinisyenin ayırıcı tanı listesi geniş olmalıdır. Kapsamlı öykü ve fizik muayeneye ek olarak seçilecek uygun laboratuvar testleriyle birlikte klinik izlem çocukluk çağında artrit nedenlerini aydınlatmaya yardımcı olabilir

Anahtar kelimeler: artritler;çocukluk çağı; etyoloji

Introduction

Arthritis is simply defined as inflammation of a joint that may affect one or more joints and often is accompanied by swelling, tenderness and pain with movement. The pathophysiology of this inflammatory process varies depending on the underlying cause [1].

Frequent clinical examination for potential diagnostic clues, timely use and interpretation of laboratory or imaging tools are crucial for the diagnosis and early treatment of patients with arthritis [2]. The aim of the present study was to evaluate the etiologies, diagnostic approach, clinical and laboratory data of patients with arthritis in a Turkish tertiary care teaching hospital in children.

Material and Methods

We reviewed the medical records of children who were admitted to the pediatric clinic with a diagnosis of arthritis. Our study covered 306 patients who were hospitalized at the pediatrics wards of Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital due to arthritis etiology between January 2008 and December 2013. Our study does not include patients with only arthralgia. The study was approved by Institutional Review Board and we received informed consent from the parents of the patients.

We noted patient's age, sex, detailed medical history and physical examination findings, the results of laboratory investigations including complete blood count [CBC], peripheral smear, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], blood chemistry tests, urine analysis, blood and urine bacterial cultures, synovial fluid cultures, serological results of Hepatitis viruses, Human immunodeficiency virus, salmonella, M. Pneumonia, varicella, Epstein-Barr virus [EBV], parvovirus, rubella, yersinia, campylobacter, brucella and

synovial fluid analysis results, antibodies including HLA B27, antinuclear antibody [ANA], anti-double stranded deoxyribonucleotide [Anti-dsDNA] and duration of diagnosis.

An arthritis which lasts longer than 6 weeks, is defined as chronic arthritis. Monoarthritis is the inflammation which is limited to one joint. Oligoarthritis is defined as the arthritis which includes fewer than five joints. Polyarthritisis is defined as the arthritis includes five or more joints. Active substance growth and bacterial appearance by gram staining in the synovial fluid culture or observing purulent fluid during synovial fluid aspiration was considered as septic arthritis [2,3].

The criteria recommended by Ayoub were used for the diagnosis of post-streptococcal reactive arthritis [PSRA] and reactive post-infectious arthritis was classified as arthritis, which lasts 6 weeks and is not associated with an infection [4]. Criteria specified by the American College of Rheumatology were used for the diagnosis of Henoch Schonlein Purpura [HSP] arthritis and Familial Mediterrenean Fever (FMF) and the Durban classification criteria were used for the diagnosis of juvenile idiopathic arthritis [JIA] [5,6]. Systemic lupus erythematosus [SLE] was diagnosed according to the diagnostic criteria of the

American Rheumatism Association [7,8]. As a result of evaluations, the patients with arthritis were divided into 5 groups including ARF/PSRA, CTD, reactive arthritis [RA], septic arthritis [SA] and brucellar arthritis [BA].

Statistical analysis was performed in SPSS for Windows 20.0 [SPSS Inc., Chicago, IL, USA.]. Descriptive statistics are given as mean, standard deviation for continuous variables and frequency, percentage for categorical variables. Comparisons were performed using the t test, Mann-Whitney u test and chi-squares test where $p< 0.05$ was considered as statistically significant.

Results

Of the patients, 51.6% [n=158] were female and 48.4% [n=148] were male. There was no significant gender difference between the diagnostic groups [p=0.759]. Average age of patients was 118 months. The average age of patients with CTD was found significantly higher than the patients diagnosed with ARF/PSRA [128±11 months, 104±19 months, p=0.012 respectively] [see Table 1].

Tablo 1. Demographic datas

Diagnosis	Age at diagnosis (month)	Duration of diagnosis (day)	Duration of treatment (day)
Collagen tissue disorders	128±11	146±12.5	115±45
ARA/PSRA	104±19	21±3.7	34±15
Septic arthritis	132±52	6±1.2	36±12
Reactive arthritis	117±67	13±2.4	11±13
Brucellar arthritis	113±48	65±6.9	52±19

Arthritis was symmetrical type in 29.4% of patients and asymmetrical type in 70.6%. The diagnoses of patiens were classified as ARF (39.2%), CTD (29%), Brucellar arthritis (13.4%), reactive arthritis (12.5%), septic arthritis (5.2%) and arthritis secondary to malignancy (0.7%), respectively. Of the patients, oligoarthritis was diagnosed in 50.7%, monoarthritis in 42.5% and polyarthritis in 6.8%. Oligoarthritis was commonly observed in patients diagnosed with CTD and ARF/PSRA and monoarthritis was commonly observed in patients diagnosed with septic arthritis, Brucellar arthritis and reactive arthritis [see Table 2].

Of the patients diagnosed with CTD; 66.3% [n=59, 59/89] were JIA, 16.9% [n=15, 15/89] were FMF, 15.7% [n=14, 14/89] were HSP, and 1.1% [n=1] were SLE. When proportioned to all patients, 19.3% were JIA, 4.9% were FMF and 4.6% were HSP.

Tablo 2. Distribution of arthritis

Diagnosis	Monoathritis n	Oligoarthritis n	Poliarthritis n	n (%)
Collagen tissue disorders	29	46	14	89 (29)
ARA/PSRA	31	83	6	120 (39.2)
Septic arthritis	14	2	-	16 (5.2)
Reactive arthritis	28	9	1	38 (12.5)
Brucellar arthritis	26	15	-	41 (13.4)
Malignancy	2			2 (0.7)
	130 (42,5)	155 (50.7)	21(6.8)	306 (100)

While 3 of the patients with septic arthritis had history of trauma, 1 was diagnosed with tuberculosis arthritis and 2 were diagnosed with septic arthritis secondary to S.aureus.

Patellar joint involvement was the most common with 62.4% [n=191] among the patients with arthritis. Hip joint involvement was significantly higher in those with Brucellar arthritis than other groups [p=0.000]. Wrist joint involvement was significantly higher in the groups with ARF/PSRA and CTD [p=0.02]. In addition, shoulder involvement was common in the CTD group [p=0.009] [Table 3].

The mean ASO levels was significantly higher in patients with ARF/PSRA than other groups [p=0.000]. Patients in ARF/PSRA group have higher CRP and ESH values when compared with patients with brucella arthritis and reactive artrhitis group [p=0.000] [p=0.003]. Average leucocyte count of ARF/PSRAgroup was significantly higher than CTD group [p=0.000] and average neutrophil percentage was found to be significantly higher in ARF/PSRA group than brucellar arthritis group [p=0.000] [Table 4].

The mean diagnosis duration of patients with CTD was 146±12.5 days. This duration was 6±1.2 days, 13±2.4 days, 65±6.9 days, and 21±3.7 days for septic arthritis, reactive arthritis, brucella arthritis and ARf/PSRA respectively. The mean of duration of diagnosis and therapy was found to be significantly longer in patients with CTD [p=0.000] [Table 1]. All patients were cured except one patient with brucellar arthritis improved with neurologic sequele.

Tablo 3. Joint involments

Diagnosis	Knee	Ankle	Elbow	Hip	Shoulder	Wrist	Hand small joint
Collagen tissue disorders	59 (%30.9)	44 (%36.4)	14 (%40)	4 (%10.8)	9 (%75)	16 (%38)	9 (%47.4)
ARA/PSRA	75 (%39.3)	50 (%41.3)	17 (%48.6)	12 (%32.3)	3 (%25)	22 (%52)	9 (%47.4)
Septic	9 (%4.7)	5 (%4.1)	0	2 (%5.4)	0	0	0
Reactive	25 (%13.1)	9 (%7.4)	3 (%8.6)	5 (%13.7)	0	2 (%4.8)	1 (%2.6)
Brucellar	23 (%12)	13 (%10.7)	1 (%2.9)	14 (%37.8)	0	2 (%4.8)	0
Total	191	121	35	37	12	42	19

Table 4. Laboratory Findings Of Groups

Diagnosis	leucocyte count (mm3)	neutrophil percentage (%)	ESR (mm/h)	CRP (mg/dL)	ASO (TU
Collagen Tissue Disorders	10.298±5744	48.1±6.4	58.5±67	42±17	126±11
ARA/PSRA	11.615±3957	44±10.5	76.3±39	61.9±69	774.9±628
Septic	11.900±2390	50.6±11	52±49	51.4±45	139±14
Reactive	10.528±1125	49.4±3.4	46.4±32	37±7	137.3±24
Brucellar	8.852±4782	40.2±12	54±28	26.7±13.5	93.5±34

Discussion

The assessment of a child with arthritis needs to differentiate conditions of varying severity, especially those that require urgent medical intervention because of suppurative infections and risk of causing permanent disability in children. Due to a lot of differential clinical pictures of childhood arthritis, it is difficult to establish a specific diagnosis and there is no standardized diagnostic approach for working up arthritis in children.

Prevalence for any musculoskeletal problem was known significantly higher in males than females in worldwide. It was also concluded that infectious arthritis was more common in males and toxic synovitis was more common in females [9]. Autoimmune diseases are more common in females, probably for the different hormonal levels, being estrogens strongly implicated in the development of autoimmunity [10]. In our study we found no difference in groups regarding diagnosis distribution according to gender.

The causes of arthritis in our study were ARF, CTD, brucellar arthritis, reactive arthritis and malignancy in descending frequency. In literature, toxic synovitis is stated to be the most common arthritis etiology in outpatients [9,10]. We conducted our study in patients who were hospitalized so that we excluded toxic synovitis patients. ARF may have different clinical manifestations in different countries according to genetic predisposition, prevalence of rheumatogenic strains, social and economic conditions. There are also differences in the prevalence of Jones criteria on different continents which may be explained by epitopes of rheumatogenic streptococcal strains and genetics. The estimated incidence rate of acute rheumatic fever was 7.4/100,000 in the Central Anatolia region [11,12]. PSRA is defined as arthritis in one or more joints in a patient who does not fulfill the Jones criteria for a diagnosis of ARF. Some authors consider PSRA as part of the spectrum of ARF, while other authors consider it as a different entity [13]. The most common cause of arthritis was ARF/PSRA in our study and its frequency was approximately 40%. This frequency is much higher than the values given in the literature. We think that the reason for this finding is the existence of a 3rd level children's cardiology clinic in our hospital which many patients were referred from the surrounding cities.

The second common cause of arthritis in our study was CTDs. Approximately 70% of this group had JIA and 17% had FMF. Similar studies in the literature also stated that JIA was the most common disease in CTD category [14]. Since FMF is a prevalent disease in our country, its high frequency was an expected result [15].

Brucellosis infection remains a serious public health problem in Turkey as well as in the other developing countries. Brucellosis

can be confused with other disorders due to the indefinite complaints like fever, arthritis, back pain, and weakness. Therefore, especially in the countries where brucellosis is common, fever accompanied by hip and lumbar pain should be important in the differential diagnosis [16,17]. We diagnosed brucella arthritis in 13.4% of the cases in our study and it may be due to high suspicion of infection. The other agents commonly associated with reactive arthritis include: Salmonella spp, Shigella, Yersinia, Campylobacter, Clostridium difficile, Chlamydia spp, Escherichia coli, Ureaplasma urealyticum, and Mycoplasma genitalium [18,19]. Among the agents who were diagnosed with reactive arthritis in our study, 3 of them had varicella, 2 of them had M. pnömonia, 4 of them had EBV, 2 of them had Parvovirus B19 and 1 of them had salmonella. In the study of Riise et. al., infection evidence was found in only 27% of the patients [9]. We think that the microbiological etiology of classical reactive arthritis would get varied with investigations that allow fast and detailed microbiological examination. In our study 3 of the patients were diagnosed with septic arthritis secondary to trauma, 1 was diagnosed with tuberculosis arthritis and 2 were diagnosed with septic arthritis due to S.aureus.

Arthritis affected the large joints mostly the knee joints as in the literature in our study [2,9]. There is overlap between causes of monoarticular and polyarticular pain and swelling. Single joint involvement was commonly seen with bacterial infections [e.g. septic arthritis and osteomyelitis] and significant trauma [e.g., fracture or hemarthroses] Other common causes of monoarticular pain and/or swelling include osteonecrosis [i.e. Legg-Calvé-Perthes disease], oligoarticular JIA, Lyme arthritis and malignancy. Multiple joint involvement could be seen with collagen tissue disorders, such as SLE, JIA and inflammatory bowel disease-associated arthritis [2,3]. In our study, CTD and ARF/PSRA were associated with oligoarticular involvement where infection-related arthritis groups [septic arthritis, reactive arthritis, and brucella arthritis] were characterized by monoarthritis. We thought that the rarity of malignancy in our study in contrast to other series; is the result of high suspicious and early diagnose of these patients in emergency department.

Since arthritis can be a finding of a lot of diseases, laboratory data alone can not be relied for diagnosis in children who apply with arthritis. The mean ASO levels of ARF/PSRA cases, which is the largest group in our study, was found to be significantly higher than the other groups. The CRP level of ARF group was found to be significantly higher only than brucella group. The comparison of groups according to the sedimentation values revealed that there was a statistically significant difference only between ARF and reactive arthritis groups. The leucocyte count comparison among the groups revealed that the only significant difference was between CTD and ARF groups and it was in favor of ARF group. Considering the diversity of the groups, it was obvious that many of the laboratory parameters alone were not enough to differentiate the groups. Potentially diagnostic clues on initial evaluation should be used as aguideline for the second step of laboratory evaluation and studies further radiological and invasive procedures. After routine non invasive investigations are recommended in patients in diagnostic algortym, we performed invasive investigations for example synovial fluid analysis in children with acute septic arthritis with low diagnostic yield. We committed that invasive investigations may be helpful relevant to the each case clinically and also in CTD group that were diagnosed based on diagnostic criteria, clinic course and excluding the other diseases, serial clinical examinations and regular follow-up is crucial.

Conclusion

Arthritis can be a manifestation of systemic disease processes in children. Appropriate diagnosis and management of pediatric arthritis can facilitate prompt recovery and prevent debilitating consequences. Therefore, the clinician must consider a broad differential diagnosis, keeping a high degree of suspicion for diseases that may have serious consequence. Complete and thorough history and physical examination in addition to clinical follow-up and diagnostic clues in laboratory may help to brighten the etiology of arthritis in childhood.

Declaration of conflict of interest

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References

1. Tan A, Strauss VY, Protheroe J, Dunn KM. Epidemiology of paediatric presentations with musculoskeletal problems in primary care. BMC Musculoskelet Disord 2018; 19:40.
2. Kimura Y, Southwood TR. Evaluation of the child with joint pain and/or swelling. https://www.uptodate.com. 2018.
3. Cavkaytar O, Düzova A, Tekşam O and et al. Final diagnosis of children and adolescents with musculoskeletal complaints. Minerva Pediatr 2017; 69:50-58.

4. Selmi C, Gershwin ME. Diagnosis and classification of reactive arthritis. Autoimmun Rev 2014; 13: 546-49.
5. Yang YH, Yu HH, Chiang BL. The diagnosis and classification of Henoch-Schönlein purpura: an updated review. Autoimmun Rev 2014; 13: 355-58.
6. Pilkington C, Tjärnlund A, Bottai M and et al; members of the IMCCP International Myositis Classification Criteria Project. Progress report on the development of new classification criteria for adult and juvenile idiopathic inflammatory myopathies. Arthritis Rheumatol 2014; 66: 70.
7. Burke RJ, Chang C. Diagnostic criteria of acute rheumatic fever. Autoimmun Rev 2014; 13: 503-7.
8. Stephenson JL, Shipman AR. The Systemic Lupus International Collaborating Clinics criteria have replaced the American College of Rheumatology guidelines for the diagnosis of systemic lupus erythematosus. Clin Exp Dermatol 2014; 39: 431-32.
9. Riise QR, Handeland KS, Cvancarova M and et al. Incidence and Characteristics of Arthritis in Norwegian Children: A Population-Based Study Pediatrics 2008; 121: 299-306.
10. Cattalini M, Soliani M, Caparello MC and et al. Sex differences in Pediatric Rheumatology. Clin Rev Allergy Immunol 2017.
11. Narin N, Mutlu F, Argun M and et al. Incidence and clinical features of acute rheumatic fever in Kayseri, Central Anatolia, 1998-2011. Cardiol Young. 2015; 25: 745-51.
12. Boyarchuk O, Boytsanyuk S, Hariyan T. Acute rheumatic fever: clinical profile in children in western Ukraine. J Med Life 2017; 10: 122-26.
13. Sato S, Uejima Y, Suganuma E and et al. A retrospective study: Acute rheumatic fever and post-streptococcal reactive arthritis in Japan. Allergol Int 2017; 66: 617-20.
14. Olaosebikan BH, Adelowo OO, Animashaun BA and et al. Spectrum of paediatric rheumatic diseases in Nigeria. Pediatr Rheumatol Online J 2017; 15:7.
15. Aksu K, Dokuyucu O, Ertenli AI and et al. Cost of Familial Mediterranean Fever [FMF] Disease In Turkey. Value Health 2015; 18: 666.
16. Parlak M, Akbayram S, Doğan M and et al. Clinical manifestations and laboratory findings of 496 children with brucellosis in Van, Turkey. Pediatr Int 2015; 57: 586-89.
17. Bosilkovski M, Kirova-Urosevic V, Cekovska Z and et al. Osteoarticular involvement in childhood brucellosis: experience with 133 cases in an endemic region. Pediatr Infect Dis J 2013; 32 :815-19.
18. Yu DT, Van Tubergen A. Reactive arthritis 2018.
19. Di Loreto S, Fabiano C, Nigro G. High prevalence of streptococcal or Epstein-Barr virus infections in children with acute non-septic monoarthritis. New Microbiol 2014; 37:81-86.